AMENDMENTS TO THE SPECIFICATION:

Please replace the second paragraph at page 10 by following amended paragraph:

"**Figure 1:** Construction of a soluble form of PHEX. Figure 1A (construct 1) represents the schematic structure of the native membrane-bound form of the enzyme and the construct in which the POMC signal peptide has been fused in frame with the ectodomain of the native enzyme (construct 2). Figure 1B represents the construct where part of the sequence for the hydrophobic transmembrane domain in construct 1 (SEQ ID NO: 2) (underlined) has been replaced by the more hydrophilic domain in construct 2 (SEQ ID NO: 3). In construct 3 (SEQ ID NO: 4), part of the hydrophobic sequence has been deleted in addition to insertion of the hydrophilic sequence as in construct 2 (SEQ ID NO: 3)."

Please replace the third paragraph at page 10 by following amended paragraph:

"**Figure 2:** Amino acid sequence of human PHEX (SEQ ID NO: 1). The boxed sequence represents the hydrophobic signal peptide/transmembrane domain. The underlined sequence represents the segment used for making the *E. coli* GST-fusion protein for monoclonal antibody production."

Please replace the third paragraph at page 24 by following amended paragraph:

"Replacement of part of the transmembrane region (underlined sequence in Figure 1B: ~~sequence~~ construct 1 (SEQ ID NO: 2)) by the underlined sequence shown on ~~line~~ construct 2 (SEQ ID NO:3) resulted in the secretion of a soluble form of PHEX from transfected COS-1 cells (results not shown). The yield was further increased by

deleting the sequence LFLV at the junction between the transmembrane and ectodomain (panel B: ~~sequence~~ construct 3 SEQ ID NO: 4). Figure 4 (lane 4) shows the amount of recombinant protein secreted in the incubation medium by transfected COS-1 cells. The same vector was also transfected in LLC-PK1 cells as described in Methods and stable transfectants were selected for their G-418 resistance. This pool of G-418 resistant cells was found to secrete substantial amounts of secPHEX (up to 600 µg/L) as seen by Western blotting (results not shown). SecPHEX was resistant to endo H, indicating that it had acquired terminal sugars, most probably during its transit through the Golgi apparatus (results not shown). The enzyme secreted by cultures of LLC-PK1 cells could then be purified either by immunoaffinity or by ion-exchange chromatography."

Please replace the first paragraph at page 29 by following amended paragraph:

"The immobilized secPHEX-EC is used as a solid phase reagent for the screening of PHEX inhibitors. Enzymatically inactive variants of this material is also prepared by binding a form of secPHEX-EC carrying a mutation on the catalytic glutamic acid residue in position ~~582~~ 581 to change it into a valine. A similar mutation in the coding sequence of NEP was previously shown to result in a catalytically inactive enzyme that nevertheless retained its full binding activity for inhibitors and substrates (Devault et al., 1988). Such an affinity reagent is used to bind and purify PHEX peptide substrates in crude tissue extracts. Receptors, if any, can be found using the same approach. Screening of inhibitor components can also be performed, although an active PHEX may be preferred. Tissue extracts prepared as described above are incubated under constant agitation in a buffer such as 0. 1M Bis-Tris pH 7.5 with 1 ml of the affinity resin at 4°C. After washing in the same binding buffer, the bound peptides can be eluted from the gel by either raising or lowering the pH and/or by increasing the ionic strength of the buffer. Many other mutations may be envisaged, the purpose of which remains the replacement or elimination of the glutamic acid residue which is specific to the gluzincins. For example, valine has been tried with success as a substituting amino

acid, but other amino acids such as hydrophobic, and preferably aliphatic, amino acids may be equivalent."